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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,412	05/30/2007	Rolf Baenteli	33711-US-PCT	1935

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

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10/22/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,412	BAENTELI ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18* is/are pending in the application.

4a) Of the above claim(s) *1-3,8-12,15,16 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-7,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/26/2006 and 12/21/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

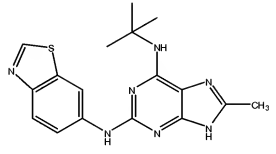
Formal Matters

Claims 1-16 and 18 are pending.

Election/Restrictions

Applicant's election without traverse of Group II, claims 4-8, 13-14, and 16, in the reply filed on 7/27/2009 is acknowledged.

Applicant's further election of the species N*2*-Benzothiazol-6-yl-N*6*-tert-butyl-8-methyl-9H-purine-2,6-diamine is acknowledged. Applicants are requested to confirm that the following compound is the elected specie (*i.e.*, Example 25 in Table 6):



N^2-(benzo[*d*]thiazol-6-yl)-N^6-*tert*-butyl-8-methyl-9*H*-purine-2,6-diamine

Claims 1-3, 9-12, 15, and 18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/27/2009.

Claims 8 and 16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/27/2009.

Accordingly, claims 4-7 and 13-14 are presently under examination and are the subject of this Office Action.

Priority

This application is a 371 of PCT/EP05/003521, filed 4/4/2005, and claims priority to Great Britain Application No. 0407723.6, filed 4/5/2004.

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statements filed 9/26/2006 and 12/21/2006. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-7 and 13-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1) The limitation "small cycloalkyl" as recited in claim 4 is a relative term whose metes and bounds are not clear. While the specification defines "small cycloalkyl" to mean C_3-C_6 cycloalkyl having 3-5 ring carbon atoms, Applicants are reminded that limitations from the specification are not imported into the claims;

2) Claims 5 and 6 recite substituent definitions followed by "e.g.". It is unclear whether "e.g.", which is interpreted to mean "for example" is intended to limit the claim to the substituents following "e.g.". As an example, when the claim recites the substituent "phenyl or phenyl substituted with lower alkyl, e.g. methoxy", it is unclear whether the substituent is limited to phenyl or phenyl substituted with methoxy, or whether other lower alkyl substituents are permitted. The limitation "such as" is also indefinite because it is not clear whether the substituent is limited to the group following "such as" or whether the substituent is only provided as a non-limiting example;

3) Claim 5 recites selections of R_6, but additionally recites that R_6R_6N is piperazinyl substituted with pyridine or pyrazine. It is not clear which R_6 definition is intended to be

controlling because it is not recited in the claim that the definition of $R_6R'_6N$ is an alternate substitution option;

4) Claim 6 recites the limitation "preferably 2-3" following the limitation n is 1-4. It is unclear whether "preferably 2-3" is intended to limit the n selection to 2-3.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-7 and 13-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to compounds of Formula (I) as disclosed in the specification at pages 3-6 and 8-18 and recited in instant claims 4-7 and 13-14. Applicants disclose that the compounds of Formula (I) disclosed in the specification and recited in the instant claims are useful in the treatment of proliferative disease (page 1) such as proliferative diseases depending on topoisomerase II (page 8). Disclosed diseases intended to be treated with the disclosed compounds include hyperproliferative conditions such as leukemias, hyperplasias, fibrosis (especially pulmonary, but also other types of fibrosis, such as renal fibrosis), angiogenesis, psoriasis, atherosclerosis and smooth muscle proliferation in the blood vessels, such as stenosis or restenosis following angioplasty. Proliferative diseases also include tumors with low levels of topoisomerase II activity. Preferred diseases include benign or especially malignant tumor, more preferably carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach (especially gastric tumors), ovaries, colon, rectum, prostate, pancreas, lung (especially SCLC), vagina, thyroid, sarcoma, glioblastomas, multiple myeloma or gastrointestinal cancer, especially

colon carcinoma or colorectal adenoma, or a tumor of the neck and head, an epidermal hyperproliferation, especially psoriasis, prostate hyperplasia, a neoplasia, especially of epithelial character, preferably mammary carcinoma, or a leukemia. Most preferred are breast tumors with over-expressed ErbB-2 and low topoisomerase II levels (page 19).

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As illustrative of the state of the art, the examiner cites Sausville *et al.* (Cancer Research, 2006, vol. 66, pages 3351-3354) and Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431).

Sausville *et al.*, cited for evidentiary purposes, teaches that traditionally explored tumor model systems are insufficient to predict how actual human beings will respond to treatment in the clinic (page 3351, left column). Even when drugs with evidence of anticancer activity in preclinical *in vivo* models are given their maximum tolerated dose in humans, they frequently fail to produce useful activity in humans (*id.*). Also, with regard to unpredictability, Johnson *et al.*, also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an

area is, the more specific enablement is necessary in order to satisfy the statute. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects.

These articles plainly demonstrate that the art of treating cancer, particularly in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers.

2. The breadth of the claims

The claims are extremely broad insofar as they are drawn to a plethora of compounds of Formula (I) having a multitude of possible substituents at the R_2, R_6, and R_8 positions.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no working examples demonstrating that any compound of Formula (I) has *in vivo* therapeutic activity against any proliferative disease.

The specification provides an *in vitro* ATPase assay to monitor ATP hydrolysis to determine the inhibition potential of the disclosed compounds on TOPO II ATPase activity (pages 20-21).

The specification provides an *in vitro* human topoisomerase II at page 21.

Table 6 of the specification discloses 74 examples of compounds of Formula (I) and provides their topoisomerase II inhibition data. The percent inhibition values given in the Table are after incubation with 10 μM of a compound of the invention. According to the legend on page 52, a "-" indicates that the given compound results in less than 50% at 10 μM. Over half of the tested compounds (44/74) resulted in less than 50% inhibition of topoisomerase II *in vitro* at a dose of 10 μM.

The specification provides only very general guidance with regard to doses and administration regimens necessary to treat all of the various proliferative diseases claimed, particularly in humans. In this regard, Applicants disclose that the dose of a compound of Formula (I) will be 3 mg to 10 g for human patients (page 28).

There is no working example of treatment of any proliferative disease in cells, animals or man. The topoisomerase II assay provides evidence that some (less than 50%) of the present compounds of Formula (I) inhibit topoisomerase II more than 50% at a dose of 10 μM *in vitro*. However, inhibition of a receptor does not predictably correlate to clinical efficacy. Thus, there are no working examples correlating inhibition of topoisomerase II with efficacy in the treatment of a proliferative disease using the claimed compounds (*i.e.,* Applicants have not shown that inhibition of topoisomerase II with a compound of the invention correlates to *in vitro* and/or *in vivo* efficacy against a proliferative disease with the same compound).

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed genus of compounds could be predictably used as a treatment for all cancerous cell growth mediated by RAF kinase as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because some of the instantly claimed compounds of Formula (I) inhibit topoisomerase II *in vitro* then the broad scope of compounds of Formula (I) must therefore, *a priori*, be useful in the treatment of proliferative diseases. However, the claims encompass a multitude of compounds (perhaps millions) having a plethora of chemically and biologically distinct substituents. Applicants tested 74 compounds having a limited number of substituents at the R_2, R_6, and R_8 positions (see Table 6). For example, 29 of the 74 compounds had a **benzothiazol-6-yl** group in the R_2 position; 37 of the 74 compounds had a **t-butyl** group in the R_6 position; and 47 of the 74 compounds had a **hydrogen** at the R_8 position.

It is evident that a very small percentage of the claimed compounds were actually synthesized and tested (for inhibition of topoisomerase II *in vitro*) by Applicants and all of the

synthesized compounds were closely related in structure having a limited number of distinct substituents compared to the broad scope of possible substituents encompassed by the claimed compounds of Formula (I). Thus, the compounds actually synthesized and screened by Applicants do not correlate in scope with the claimed subject matter. Given the extremely diverse compounds encompassed by the claims and the limited examples provided in the specification, the skilled artisan cannot predict what structural features (other than those of the compounds actually synthesized and tested) are important for inhibition of topoisomerase II. This is especially true when one considers that over half of the tested compounds (44/74) resulted in less than 50% inhibition of topoisomerase II *in vitro* at a dose of 10 μM.. In other words, the structure activity relationship demonstrated in the examples is limited to a very small sub-genus of compounds.

Determining if any particular claimed compound would treat any particular proliferative disease state would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants. As noted *supra*, even *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since enable a patentable use of the claimed compounds of Formula (I) a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614